agus. The exact prevalence is not known, but Barrett's esophagus is found in about 10% of patients undergoing esophagoscopy for symptoms of reflux.

On histologic examination, Barrett's esophagus has a heterogeneous appearance and comprises a variety of cell types similar to gastric and intestinal epithelial cells. A distinctive histologic pattern of goblet cells interspersed among columnar mucous cells is common and virtually diagnostic of Barrett's esophagus. Other patterns resemble gastric fundic or cardiac mucosa and can thus be interpreted as Barrett's esophagus only when the site of biopsy is definitely the esophagus and not a hiatus hernia.

This condition is clinically important because of its association with esophageal adenocarcinoma. In recent studies, a 30 to 40 times increased risk was estimated when Barrett's esophagus is present. Because these figures are based on a relatively short follow-up period, the actual risk may be even higher. Such considerations have led to the suggestion that biopsies be done regularly on patients with Barrett's esophagus to look for epithelial dysplasia, which, as a putative precursor of adenocarcinoma, would serve to identify those patients at highest risk for malignancy. Problems with this suggestion include the lack of well-defined histologic criteria for recognizing dysplasia and distinguishing it from reactive or regenerative changes. Nevertheless, high-grade dysplasia has recently been shown to represent a morphologic marker of risk for esophageal adenocarcinoma.

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The Carcinoma-Carcinoid Spectrum

IN THE PAST DECADE we physicians have become aware that carcinoid tumors show a much wider clinicopathologic spectrum than previously thought. This has given rise to a plethora of new terms, some of which, such as apudoma, neurochristoma and neuroendocrinoma, are based on their postulated neuroectodermal derivation; others, such as neuroendocrine carcinoma, on their clinical behavior, and a group, such as gastrinoma, on their secretion products. Because these tumors are morphologically distinctive, I see no point in changing Obendorfer's original terminology, and thus I designate these lesions as carcinoids and specify their differentiation and secretion products (Table 1).

On histologic examination, some tumors may show atypical features such as glandular profiles, a spindle cell pattern, squamous or osteoid metaplasia or pleomorphism with frequent mitoses and necrosis. In rare cases they may be poorly differentiated and resemble undifferentiated large-cell or small-cell carcinoma (oat cell carcinoma) and lymphoma. As is well known, some carcinoids are associated with well-defined syndromes, such as the carcinoid or the Zollinger-Ellison syndromes, due to the secretion of amines or peptides. Immunohistochemical analysis of these tumors has shown that, whereas one amine or peptide may predominate, such as serotonin or gastrin, most are multihormonal. These findings

TABLE 1.—*Nomenclature and Classification of Pure and Mixed Endocrine Cell Tumors*

Carcinoid tumors
Well differentiated
Moderately differentiated
Poorly differentiated
Small cell (oat cell)
Large cell
Mixed (composite) glandular-endocrine cell carcinoma
Microglandular-goblet cell carcinoma
Scirrhous-argyrophil cell carcinoma
Adenoendocrine cell carcinoma
Amphicrine cell carcinoma

are also seen with the clinically silent carcinoids such as the foregut and hindgut tumors. Furthermore, the immunohistochemically shown amines and peptides in the primary tumor do not necessarily correspond to those found in the overlying endocrine cells or in metastatic lesions.

Although the presence of scattered endocrine cells within adenomas and carcinomas of the gastrointestinal tract has been known for some time (in as many as 20% of all colonic carcinomas), there are a number of tumors in which there is a large admixture of endocrine and epithelial cells. Thus, the strict separation of gut mucosal tumors into carcinoma and endocrine tumors has had to be modified to include those tumors with admixtures of varying proportions of endocrine and epithelial cells. These tumors have been designated as mixed or composite tumors and have been further subdivided into several distinctive histologic types (see Table 1). Some of these tumors, such as the microglandular-goblet cell carcinoma, have a distinctive clinical behavior, whereas others, such as the scirrhous-argyrophil and adenoendocrine cell carcinoma, appear to behave in a manner similar to the corresponding carcinoma. Finally, there is a further distinctive tumor type, namely the amphicrine tumors. These differ from the mixed tumors in that endocrine and epithelial cell constituents are present within the same cell. These findings support the hypothesis that epithelial and endocrine cells of the gut share a common cell of origin.

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Lymphocyte Gene Rearrangements—A New Technique in the Diagnosis of Lymphoma

THE HISTOPATHOLOGIC DIAGNOSIS of lymphoma can be difficult, particularly when the disease presents at extranodal sites. Conventional microscopic or immunohistochemical studies often prove inadequate for the evaluation of T-cell infiltrates, of neoplasms lacking appreciable atypia or where a superimposed inflammatory process obscures the underlying malignant process.

Recent insights into the molecular biology of lymphocytes have led to the development of a technique that provides an objective estimate of the clonal composition of lymphoid in-

filtrates. Almost all lymphomas are monoclonal populations, the progeny of a single transformed progenitor cell. Reactive infiltrates, in contrast, are polyclonal. The clonality of a lymphoid cell population can be determined by analyzing the structure of genes that code for immunoglobulins in B cells or for the antigen receptor molecules of T cells. These genes undergo precise rearrangements during lymphocyte development, assuming a different structure in each clone of lymphoid cells. By evaluating the type and number of such rearrangements in DNA extracted from a clinical biopsy specimen, the presence of any predominant B- or T-lymphocyte clone can be readily detected. When present, such clonal proliferation implies malignancy. Clonal populations constituting as few as 5% of the infiltrating cells can be shown by this method. Several researchers have shown that the pattern of gene rearrangements present in a lymphocyte population also gives evidence of its lineage (T versus B cell) and degree of differentiation.

Because cutaneous lymphoid infiltrates represent a notoriously difficult diagnostic problem, we applied this technique to a broad spectrum of such lesions. Skin biopsy specimens of mycosis fungoides, a cutaneous T-cell lymphoma, were found to contain a monoclonal T-cell infiltrate, as did the peripheral blood of patients with Sézary's syndrome, a form of chronic T-cell leukemia. Clonal T-cell proliferation has also been identified in several rare conditions whose relationship to T-cell lymphoma is controversial, such as lymphomatoid papulosis and granulomatous slack skin. This technique also permitted reliable distinction between the polyclonal lesions of cutaneous pseudolymphoma and the monoclonal infiltrates of cutaneous B-cell lymphoma. The analysis of gene rearrangements can therefore provide both scientific insights and an objective diagnostic aid in the evaluation of lymphoid cell infiltrates of the skin.

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Hodgkin's Disease—Controversies 1986

THE CELL OF ORIGIN in Hodgkin's disease remains a mystery, but recent data from a number of laboratories shed additional light on the subject. The issue is of more than academic interest because it also involves the question of the role of markers in the diagnosis of Hodgkin's disease. The morphologic diagnosis of Hodgkin's disease is relatively noncontroversial, but there is a surprising error rate in diagnosing Hodgkin's disease. A recent study found an error rate of 13%. This figure would appear to be unacceptable given the current level of therapeutic success with this disease.

The antibody Leu M1, originally defined as a myelomonocytic marker, has been increasingly utilized as a marker of Hodgkin's disease following a number of recent reports of its presence in Reed-Sternberg cells and their variants. Two major questions have arisen over these data. Weak or absent staining in cases of lymphocyte-predominant Hodgkin's disease has led some authors to conclude that this disorder is unrelated to the other forms of Hodgkin's disease. But recently Hsu and co-workers have suggested that the cells are simply more mature and as a consequence have sialylated the antigen. Using neuraminidase treatment, they removed the terminal sialic acid residues and found the antibody Leu M1 was present in most cases of lymphocyte-predominant Hodgkin's disease. The second major question concerns the specificity of the reaction. The original reports found little evidence of staining for the antibody in non-Hodgkin's lymphomas, but a recent study shows that many of the peripheral T-cell lymphomas most likely to be confused with Hodgkin's disease did stain for it.

The second question above is of practical significance. Grouping the results from all of the articles in question suggests that at least a portion of peripheral T-cell lesions contain the antibody. For those with access to frozen section or plastic section immunophenotyping, the application of standard B & T reagents can generally resolve the differential. With only paraffin blocks available, there are still some markers that will help resolve the question of peripheral T-cell lymphoma versus Hodgkin's disease. These include a number of markers commonly seen in Hodgkin's disease, but seen infrequently in T-cell lymphomas, such as HLA-DR/Ia, cathepson B, lysozyme, α_1-antitrypsin, peanut agglutinin and concanavalin A.

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Monitoring Cervical Carcinoma With Fine-Needle Aspiration Biopsy

DESPITE MAJOR ADVANCES in diagnosis and treatment, cervical carcinoma continues to be a disease of major epidemiologic importance, with an estimated 16,000 new cases each year and an annual mortality of 7,000. Rational surgical or radiotherapeutic treatment of invasive cervical carcinoma depends on accurate initial staging and subsequent surveillance for occult persistent and recurrent disease. Most recurrences occur early and in areas palpable by pelvic examination. If disease has not spread beyond the central pelvis, pelvic exenteration can offer long-term survival, even in women with recurrent cervical carcinoma. Follow-up of patients with cervical cancer traditionally has been by physical examination, exfoliative cytology and radiologic examinations. Recently some have advocated adding fine-needle aspiration biopsy (FNAB) to the list of procedures that may be effective in detecting persistent or recurrent disease in patients with cervical cancer.

The principal advantages of FNAB over open surgical biopsy for following patients with cervical cancer are rapid reporting of results, minimal morbidity and complications and good patient tolerance. In women with cervical carci-